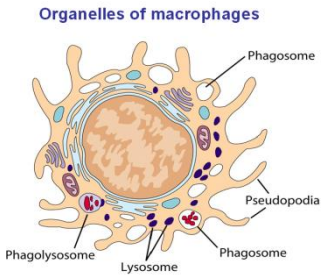
Week 4 - Heart disease

- CVD's are the leading cause of mortality.
- Structure of heart - 2 atria: thin walls, collect blood returning to heart via venous system, pump blood into ventricles. 2 ventricles: thicker walls (more powerful), pump blood to lungs (right ventricle), pump blood to the body (left ventricle) Purpose: permits stepwise increases in blood pressure as blood passes from venous to arterial vessels (increases from ~ 40 mmHg in RV to ~ 120 mmHg in LV).
- Congenital heart defects - Ventricular septal defects. Superior part of interventricular septum fails to form. Blood mixes between the ventricles but more blood shunted left to right. Coarction of aorta - part of aorta is narrowed increasing workload on the left ventricle. Tetraology of fallot - 4 abnormalities resulting in insuffieciently oxygenated blood pumped to body - narrowing of pulmonary valve, thickening of wall of right ventricle, displacement of aorta over ventricular septal defect, ventricular septal defect opening between left and right ventricles.
- Heart valves - Atrioventricular (AV) valves between each atrium and ventricle. Anchored by strong fibres that prevent them turning inside out. Pressure generated by powerful contractions of the ventricles closes AV valves, keeping blood from flowing back into atria. Semilunar valves at exits of heart (where aorta leaves LV and where pulmonary artery leaves RV). Valves open when blood is pumped into arteries following ventricular contraction. Valves close when ventricles relax so preventing blood from flowing back into ventricles
  - Bicuspid aortic valve - most common cardiac valvular anomaly - predisposes to calcification. Instead of being thrown flat against aortic wall during systole, shows a domed configuration.
  - Aortic stenosis - caused by rheumatic heart disease. If the leaflets do not close correctly, aortic regurgitation can occur. May require heart surgery.
  - Mitral valve stenosis - most commonly caused rheumatic heart disease, caused by cleft valve.
  - Treatment for valvular diseases - surgery - replacement with mechanical valves.
- Cardiac cycle - one complete sequence of heart filling and pumping.
  relaxation phase (atria and ventricles in diastole) ~ 0.4 s: blood returns from large veins and flows into atria and ventricles. Atrial systole ~ 0.1 s: forces remaining blood out of atria into ventricles. Ventricular systole ~ 0.3 s: pumps blood into large arteries.
- Heart beat - Cardiac muscle cells can contract without any signal from nervous system. Cardiac myocytes are electrically coupled (by intercalated discs between adjacent cells) so can contract in unison. The sinoatrial (SA) node, or pacemaker, maintains heart's pumping rhythm by setting rate at which all cardiac muscle cells contract. Position: within wall of RA near point of entry of superior vena cava. Function: generates electrical impulses.
  - The SA node initiates the signal, Electrical impulses spread through atrial walls that contract in unison. Impulses pass to the atrioventricular (AV) node (another region of specialised muscle tissue), a relay point between RA and RV. Impulses are delayed (~0.1 s) to ensure atria contract first and empty completely before ventricles contract (phase 2 of cardiac cycle). Specialised muscle fibres (Purkinje fibres) conduct signal to contract throughout walls of ventricle.
  - The SA node sets tempo for entire heart, but is influenced by a variety of signals and hormones via two sets of nerves that oppose each other in terms of being able to adjust the heart rate. Body temperature affects pacemaker activity (increase of 1°C raises heart rate by ~10 b/min (e.g. pulse rate increases with fever). Positive chronotropic factors increase heart rate, adrenaline (epinephrine) increases heart rate (fight-or-flight hormone released from the adrenal glands). Negative chronotropic factors decrease heart rate, b-adrenergic receptor antagonists.

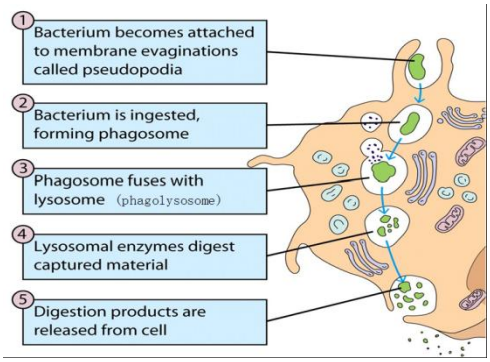
Week 7 - Immune System

How immune system works:

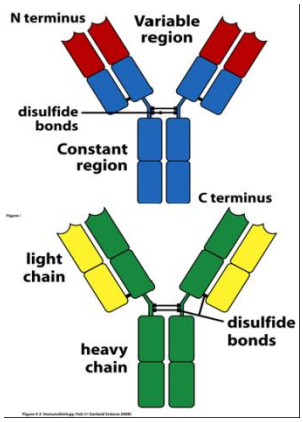
- 4 main tasks
  - Immunological recognition
  - Immune effector function
  - Immune regulation
  - Immunological memory
- Innate and adaptive immunity:
  - Innate immunity - responses are generic, occur at the same speed and efficiency each time. No memory persists afterwards. Recognise an invading pathogen. Immediate response but inefficient on its own - not enough phagocytes for speedy containment of invading pathogens.
  - Adaptive immunity - second level of defence, increases in strength and effectiveness, foreign agent is recognised in a specific manner and the immune system acquires memory of it. Memory cells produced. On primary exposure to pathogens it amplifies the immune response to contain pathogens, makes immune response more specific to particular pathogens. On secondary exposure to pathogens - makes immune response faster and better.
- Secondary immune responses - T and B cells remember that the body has come into contact with the pathogen before. Driven by memory T and B cells. Vaccines harness this property of the immune response.
- Cells of body - all derived from the bone marrow in a process called Haematopoiesis. All cells derived from a common multipotent stem cell population. Divide to either a myeloid or a lymphoid progenitor. These cells are then committed to that linage.
- Anatomy of immune system - Immune cells are organised intro lymphoid organs. Primary lymphoid organs, e.g. Bone marrow, thymus - immune cell development. Secondary lymphoid organs e.g. Spleen, tonsils - immune responses generated.
- Innate immunity - Phagocytosis occurs - carried out by macrophages, neutrophils, dendritic cells.
  - Macrophages - innate immune cell one of the first cells that a pathogen is likely to encounter, fixed or wandering through tissues, role is to recognise pathogen and eliminate and remove dead cells by phagocytosis. Initiation of the immune response and associated inflammation.



  - Neutrophils - produced and released from bone marrow in response to infection. Circulate in blood for 10hours prior to migrating to tissue. Role is to arrive at infection site and kill cells.
  - Mast cells - 2 types mucosal in gut and lung and connective tissue cells in most tissues. Role is to be a mediator of a variety of allergic and inflammatory conditions. Activated mast cells can increase vascular permeability, vasodilation, smooth muscle cell contraction and attract neutrophils.
- Stages of phagocytosis:
  - Recognition and attachment
  - Ingestion
  - Killing
  - Degradation
  - Exocytosis



- Adaptive immunity - B and T cells. 2 kinds of active immunity. Cell-mediated immunity - mediated by t-cell, can be transferred by t-cells. Humoral immunity - mediated by antibody - transferred by antibody, antibodies can bind exposed epitopes on antigens.



- An antigen is defined as "anything that can be bound by an antibody“ .Antibodies interact specifically with relatively small parts of molecules. These are known as antigenic determinants or epitopes. Small antigens are referred to as haptens. They are not immunogenic and need to be coupled to a carrier to elicit an immune response.
- Antibody is produced by B cells. Is produced to one specific epitope, neutralises toxins, blocks adhesion/cell entry, kills via complements, neutralises pathogen infectivity and prevents replication.
- 3 actions of antibody -
  - Neutralisation - Block biological activity of target molecule e.g a toxin binding to its receptor.
  - Opsonisation- Interact with special receptors on various cells, including macrophages, neutrophils, basophils and mast cells allowing them to "recognise" and respond to the antigen.
  - Complement Activation - Cause lysis by complement, also enhancing phagocytosis
- B cell recognition of antigen - B cells have surface antibodies, variable region recognises foreign antigen.
  - Memory B cells - confer immunological memory, ensuring that secondary response to pathogen is rapid.
  - T cells - produced in bone marrow, activation - different t cells express distinctive membrane molecule, all t cells express the t cell receptor. Different types - CD4 and CD8.
  - CD4 - Helper t cells express this as an adhesion molecule, responds to exogenous antigen. Role is to provide help for effector cells. Promotes macrophage activation and causes B cells to produce antibodies.
  - Cytotoxic t cells express adhesion molecule CD8, respond to intracellular antigen. Function is to recognise and lyse virally infected or tumour cells.
- T cells recognise antigen via the T cell receptor. The T cell receptor is unable to recognise antigen in the same way as the B cell receptor on B cells. The T cell receptor only recognises antigens in the form of peptides bound to MHC molecules.
  The T cell receptor can only recognise peptides complexes with MHC molecules

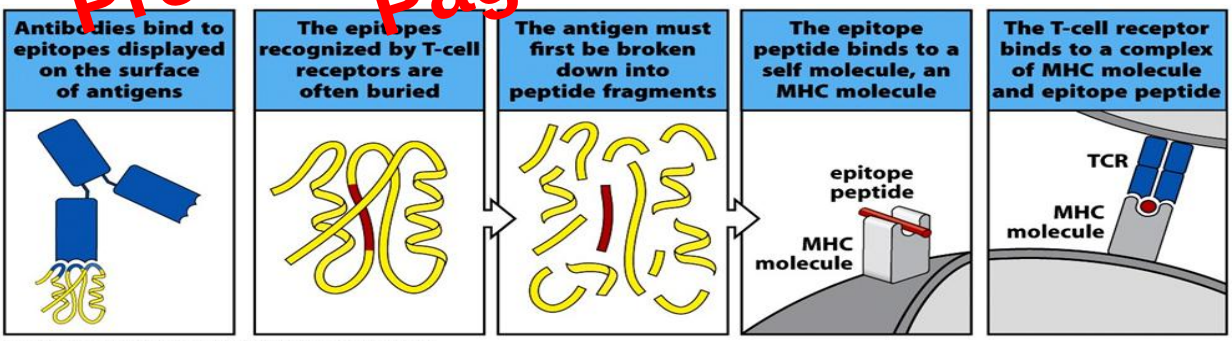
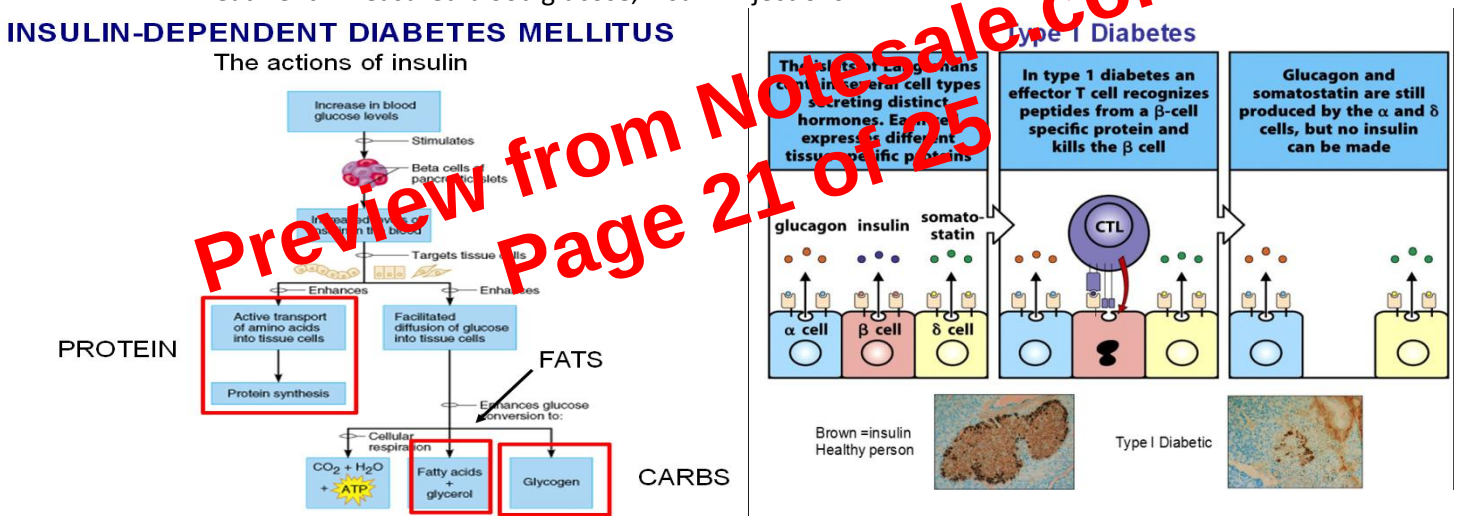


Figure 1-16 Immunobiology, 7ed. (© Garland Science 2008)

Diseases of immune system:

- When immune system fails to attack - immunodeficiency's
- When the immune system attacks self - diabetes, myasthenia gravis, MS, Rheumatoid arthritis.
  - Immunodeficiency - when immune system is depressed or absent and an individual is unable to mount a normal immune response to protect the body.
- Origins of immunodeficiency:
- Primary or congenital - Inherited genetic defects in immune cell development or function or inherited deficiency in a particular immune molecule.
- Secondary or acquired - a loss of previously functional immunity due to infection, radiation, splenectomy, aging, malnutrition or drugs.

- Autoimmunity - occurs when the immune system mistakenly attacks self proteins. Involves similar mechanisms to those used to attack pathogens. Autoimmune diseases can be organ specific or systemic. 4 types of autoimmunity.
  - Underlying causes - circulating self-reactive lymphocytes exist, problems lies in their effective regulation.
  - Autoimmune reactions leading to autoimmune diseases can involve - autoreactive T cells and autoantibodies. Both the autoreactive T cells and autoantibodies react to proteins in the body known as autoantigens.
  - Self-tolerance - ability of immune system to not attack normal body tissues, autoimmunity is therefore regarded as a breakdown in self-tolerance. Can be due to genetic factors, or environmental exposure or infections.
- Organ specific - Immune response is directed to a target antigen that is unique to a single organ or gland. Effects are limited to that organ. Causes cellular lysis and inflammatory response in target organ. Function of organ declines.
- E.g. Type 1 diabetes (Insulin-dependent diabetes mellitus) - insulin producing cells destroyed. Type 4 autoimmunity. Mechanism - T cell mediated destruction of the cells that make insulin. Auto-immune attack on insulin-producing cells; b-cells in the islets of the langerhans in the pancreas, insulin levels fall and blood glucose rises. CD8+T cells recognise a protein from insulin producing b-cells in the pancreas. B-cells are destroyed by the cytotoxic action of the CD8+T cells and cannot be produced.
  - Symptoms - Increased plasma glucose, glucose in urine, thirst, weight loss, increased urin production, increased use of fats as source of energy - increases ketones in bloodstream which can cause convulsions due to lowered blood pH.
  - Treatment - Measured blood glucose, insulin injections.



- E.g. Myasthenia gravis - Type 2 autoimmune disease - serious muscle weakness - Target antigen is acetylcholine receptors on motor end-plates of muscles. Antibodies prevent the binding and thereby the actions of acetylcholine, inhibits muscle activation. Antibody dependent mechanisms cause cellular damage leading to progressive muscle weakening.
  - Symptoms - abnormal weakness and fatigability of selected muscles, mainly facial muscles and those that affect breathing and limb movements.
  - Treatments - Acetylcholine esterase inhibitors to try and build up concentrations on acetylcholine, immunosuppressive drugs, plasmapheresis - treatment of blood plasma.
- E.g. Multiple sclerosis - Type 4 autoimmunity - Causes imflammatory lesions along myelin sheath of nerve fibres, cerebro-spinal fluid contains activated T lymphocytes that cause inflammatory lesions that destroy myelin. Disables rapid depolarisations along nerve fibres.